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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1528-332-1PC		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) FOR FURTHER ACTION	
International application No. PCT/US99/03469	International filing date (day/month/year) 17/02/1999	Priority date (day/month/year) 20/02/1998	
International Patent Classification (IPC) or national classification and IPC G06F15/80			
Applicant THE GOVERNMENT OF THE UNITED STATES OF ... et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input checked="" type="checkbox"/> Certain defects in the international application</p> <p>VIII <input checked="" type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand 20/09/1999		Date of completion of this report 07.06.2000	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Casteller, M Telephone No. +49 89 2399 2666 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/03469

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-55 as originally filed

Claims, No.:

1-65 as originally filed

Drawings, sheets:

1/11-11/11 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
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International application No. PCT/US99/03469

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-65
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-65
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-65
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

- D1: J. WATSON: "Recombinant DNA - A short course", SCIENTIFIC AMERICAN BOOKS / W.H. FREEMAN AND COMPANY, 1983, XP002108084, pages 45-54
D2: R. SCHLIEF: "Molecular recognition: Feeling for the bumps", NATURE, vol. 325, 1 January 1987 (1987-01-01), pages 14-15, XP002108081
D3: T.D. SCHNEIDER: "Sequence logos, machine/channel capacity, Maxwell's demon, and molecular computers: a review of the theory of molecular machines", NANOTECHNOLOGY, vol. 5, no. 1, 1 January 1994 (1994-01-01), pages 1-18, XP000607276

2. It is known from e.g. D1 that there exist:

a repressor molecule that binds at a DNA site called the operator (cf. figure 4-1, REPRESSOR and CONTROL SITE; page 46, left column, lines 2-4),
an enzyme molecule (e.g. RNA polymerase) that by binding at a DNA site called the promoter starts synthesis of a predetermined organic molecule (e.g. β -gal mRNA) by transcription (cf. page 46, left column, lines 6-7, right column, last two lines, page 47; left column, lines 1-4). D1 also discloses that:

when the repressor molecule binds to the operator, it sterically prevents the enzyme molecule to bind to the promoter, whereby transcription synthesis cannot start (cf. page 46, left column, lines 4-7; page 47, the sentence bridging the left and the right column);

the presence of an inducer molecule (e.g. lactose) can prevent the repressor molecule to bind to the operator in that said inducer molecule binds to the repressor molecule, thus allowing transcription synthesis to start (page 46, left column, lines 7-11).

D1 also teaches that the operator site and the promoter site are located "near" or "nearby" on the DNA double helix (cf. page 46, left column, lines 2-3, page 47, sentence bridging the left and the right column).

D2 sets out that, in a DNA sequence there can be a plurality of "closely related" binding sites, e.g. the three operator sites O_{R3} , O_{R2} , O_{R1} , to which two proteins, e.g.

Cro and a repressor, can competitively bind. Each of these two proteins can bind to each and every one of said binding sites (cf. page 14, first column, last paragraph and second column, first line).

However, the two proteins have higher affinity with and bind preferentially to different ones of said binding sites (cf. page 14, second column, lines 5-10).

Each one of these three binding sites is exactly the same for the two proteins, i.e. no one can be regarded as being in fact two separate but slightly overlapping binding sites (cf. page 14, third column, lines 11-12).

D3 (page 15, left column, lines 15-16) shows that the general idea of implementing boolean logic gates by means of organic molecules was known in the art.

Insofar actual implementation is concerned, however, it merely states that an AND function could be implemented by an enzyme verifying whether a predetermined base sequence occurs in a DNA strand, and that a NOT function could be implemented by a molecule binding to a DNA binding site which prevents another molecule from binding on the same binding site (cf. page 15, left column, lines 1-8).

3. The present invention is based on the prior art recognition that it is possible to synthesize DNA strands having nearby binding sites such that, when a protein binds to a first binding site, it prevents by sterical hindrance another molecule to bind to a second nearby binding site.

This known concept is taught e.g. in D1, where the repressor molecule, by binding to the operator binding site, sterically prevents the enzyme molecule to bind to the nearby promoter binding site.

The invention however is distinctively characterized over D1 by further teaching that this effect of preventing the binding in a nearby binding site must be symmetrical, that is, a protein binding to the second binding site also prevents by sterical hindrance another molecule to bind to the first nearby binding site.

This inventive teaching allows to implement both a flip-flop having two binding sites (independent claims 1, 34, 51) or a gate having three binding sites (independent claims 15 and 64).

Said inventive teaching can not be derived from e.g. D1, where the above mentioned inducer molecule (e.g. lactose) can prevent the repressor molecule to bind to the operator binding site, but not by binding to the nearby promoter binding site: said inducer molecule instead binds to the repressor molecule itself.

In this respect, D2 and D3 represent background prior art further away from the

invention because the binding-prevention effects therein described all relate to the case in which a second molecule can not bind to the same binding site where a first molecule is already bound.

The invention is additionally characterized by the indication that one and the same protein can bind to either one of said two nearby binding sites, whereas e.g. in D1 one only of two different proteins bind to a given binding site.

Consequently, the subject-matter set out in the present claims is considered to be novel and non-obvious with respect to the disclosures of the available prior art. It is also evident that the invention is industrially applicable.

The requirements of paragraphs (1) to (4) of Article 33 PCT are thus met.

Re Item VII

Certain defects in the international application

4. The following defects which have been noted in the present application.
At page 15, line 6, "site two bound" should probably read "site two unbound";
at page 16, line 3, delete the second "the";
in figure 4, the first NOT gate A should have both inputs I₁ labelled BS1, the second NOT gate B should have two I₂ inputs (cf. page 24, lines 20-23).
The statements after the application title at page 1 clearly stem from a corresponding American application, but are evidently irrelevant to the present international application.
Furthermore, at page 55, last paragraph, the description contains general statements that the extent of protection may be expanded in some vague and not precisely defined way. Such general statements shall have been deleted as contrary to Article 6 PCT, cf. also PCT Preliminary Examination Guidelines, C-III, 4.3a.

Re Item VIII

Certain observations on the international application

5. The application does not meet the requirements of Article 6 PCT, because independent claims 1, 15, 34, 51 and 64 are not clear.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/03469

6. Independent claim 1 and 34 in combination do not meet the requirements of conciseness and clarity because they substantially refer to the same subject-matter, but define it in two incompatible categories, namely a "system" and a "composition". It is submitted that in the present case defining two nucleic acids (the isolated one and the one with two binding sites on it) as a system appears improper and confusing. Present claim 1 (and its dependent claims) appears redundant. Furthermore, the precise length definition (a length of 3 or 5 base pairs) of the isolated nucleic acid recited in claims 34 and 51 appears superfluous, as such feature is not essential for defining the invention and should rather be included in an appropriate dependent claim or claims.
- The clarity and completeness of claims 34 and 51 would have been improved by amending their first lines to read "for storage of binary information or for regulating gene expression in cells" (cf. page 14, lines 23-24). Likewise, the initial lines of claim 64 should have been amended to read "transforming binary information or regulating gene expression in cells" (cf. page 18, lines 6-11).
- The claims should have been provided with reference signs placed in parentheses (Rule 6.2(b) PCT).
- Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

PATENT COOPERATION TREATY

EAM

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

TOWNSEND AND TOWNSEND AND CREW LLP
Attn. HUNTER, T.
Two Embarcadero Center
8th Floor
San Francisco, CA 94111
UNITED STATES OF AMERICA

59 JUL 21 AM 9:34

RECEIVED

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

15/07/1999

Applicant's or agent's file reference

15280-3321PC

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 99/03469

International filing date
(day/month/year)

17/02/1999

Applicant

THE GOVERNMENT OF THE UNITED STATES OF AMERICA as

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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Authorized officer

Lucia Van Pinxteren

DOCKETED

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.